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FIFTY YEARS IN EPIDEMIOLOGY: SOME LESSONS LEARNED

Talk given at epidemiology retirement symposium

So many thanks are due to so many people here that I would exhaust my allotted time were I just to truly acknowledge the debt I owe to so many. But let me at least single out Madeleine Lenski who so kindly and efficiently organized this truly wonderful event, along with other events this week! And my wife Ellen Pollak joined Madeleine in in developing the social events that bracket this special day. And thanks to all of you who gave us your insights and wisdom on such a range of topics today all held together by our joint desire to improve the health of the population.

And of course, as many of you know, my very presence at MSU for the past 33 years would not have happened were it not for Ellen, who received an offer of an appointment in the MSU English department that allowed me to tag along.

In the valedictory talk I gave last May, which is on our departmental website, I reminisced about the founding of our department and the fortuitous way it came about. Today I'll talk a bit about my academic career and attempt to draw some lessons that may be of use to the younger generation of scientists. By titling this talk *50 Years in Epidemiology*, I am circling the year 1972 as the point of origin.

1972 was the year I graduated from medical school and the year my first contribution to science was published, an abstract in the annual meeting of the American Thoracic Society on the topic of BCG vaccination against tuberculosis in the US. The work was done during an elective in epidemiology with Frank Speizer, the great pulmonary disease epidemiologist, an elective that changed my career focus, indeed my life, and that presentation, co-authored with Frank, was the beginning.

I took four lessons away from that experience. The first, was my discovery that a single-minded passion for a topic (which I then had for BCG vaccine) can be translated into a somewhat unique store of knowledge. My many hours in the Countway library, tracking down papers that had been cited by other papers, uncovering such gems from the 1930's as an alternate assignment trial of BCG vaccine in Algerian newborns with overall infant mortality as the outcome and a

treatment-control study with some 3,000 child participants conducted by Joseph Aronson and his wife Charlotte in Indian reservations in the West and Alaska. These important sources of strong evidence favoring BCG use had been nearly entirely forgotten, and the US public health consensus was that BCG was not useful in preventing tuberculosis. I learned then that solitary scholarly work – digging into a topic and trying to find out everything you can about it – is one of the most rewarding things you can do in academia. And the knowledge you gather is yours alone. You own the product of that kind of work. And I think I learned this lesson in part from my wife, whom I could only with difficulty pry away from the Bennington College library when I was desperately trying to interest her in a certain Dartmouth medical student.

The second lesson, which I learned to my great surprise, was that the conventional wisdom in medicine is not always correct. That same year, 1972, I interviewed for internships in pediatrics. One interview was with Horace Hodes, chair of pediatrics at Mount Sinai Hospital in New York City and one of the giants of pediatric infectious diseases in the 20th century. Noting that I had done some work on BCG vaccine, he pressed me on the topic, reminding me that the US trials of BCG vaccine, which were led, by the way, by George Comstock, later to become a famous Johns Hopkins epidemiologist, did not show effectiveness. I pointed out

that the vaccine used in those trials was later found to be of weak potency and that the trials were conducted in populations, in the US South and Puerto Rico, where early life infections with atypical myobacteria were common, providing some partial immunity to tuberculosis. To my astonishment, he ended the conversation by saying, “Well, it looks like you know more about BCG than I do”. All this from hanging around the library! What a lesson.

But the third lesson was a negative one. Although I wrote up the paper for the course, and even got a prize for it at graduation, I never published the findings. My excuse was that my internship began the month following the publication of that lonely abstract, and that 80-hour weeks and clinical preoccupations left me no time to produce a publishable paper. As the years dragged on, the topic receded into the distance. I would see Frank periodically, and he would smilingly say things like, “Nigel, you owe me a paper. It’s been, let’s see, 20 years?” The lesson here is – Finish the job! In my subsequent work I tried hard not to repeat that early mistake.

And the fourth lesson, which I will come back to later because it has resonated lately for me, is that randomized trials, especially when negative, have considerable potentially to mislead.

A more justifiable starting point for my academic career would be 1978, the year I obtained my first NIH grant. My first lesson from that experience is that ignorance really can be bliss. Had I known better, I would not have submitted an R01 application to NIH not much more than a year after completing my clinical training, my MPH not yet in hand, with no published papers, and just one abstract to my name - on a topic unrelated to the application! But I didn't know any better, and hardly anyone told me what a fool I was to apply, even though that was undoubtedly true.

I must credit the Australian physician-epidemiologist, Fiona Stanley, for setting me on the path towards that first R01. Fiona, by the way, is the elder sister of our own Bryden Stanley, Professor of Veterinary Medicine at MSU. Fiona had just completed a fellowship in London with the British epidemiologist Eva Alberman and in 1976-77 was doing a fellowship at NICHD. Eva was a close friend of my mentors Mervyn Susser and Zena Stein (about whom more later) and thus Fiona was invited to give a talk in the Epidemiology Division at Columbia. I listened with rapt attention to the research she had done on the then very new technology of newborn intensive care in a part of London. She showed among other things, that mortality was higher for small babies born at night in hospitals without newborn intensive care, but no such variation was seen in better equipped hospitals.

I wondered then whether we could examine the effectiveness of newborn intensive care in the entire population of births in New York City. I drafted a version of the study for a course in research proposal development at the Columbia School of Public Health in the Spring of 1977. The teaching assistant gave me a grade of C+. And then a colleague told me that someone had tried to study the effect of newborn intensive care on mortality in NYC and hadn't found anything and my goal was impossible.

All this negativity troubled me, and after all I was just a lowly assistant clinical professor doing general pediatrics at Jacobi Hospital in the Bronx. Part of that negativity was a skepticism I have encountered often since, about the value of vital data. We planned to obtain all of our outcome information from linked birth and death certificates. Not only are these forms of data collected on virtually everyone, they usually have a constrained set of variables that are checked carefully by state agencies for consistency and for adherence to guidelines. Electronic medical records are much less reliable and valid.

But on the other hand, Mervyn Susser, for whom I always had enormous respect, was enthusiastic about the idea and I had further support from two stellar neonatologists at Einstein - Larry Garter and Kwang-Sun Lee. I wrote my draft of

the application by hand, in script, on a yellow legal pad, but knew no one who could type it up in the format required by NIH. Sheepishly, I approached the secretary of the director of general internal medicine at Jacobi Hospital – someone not even in my department - who told me that since she was not too busy that week, she was willing to type up my grant application, which I sent to NIH in January of 1978. The application was sent from Einstein, but I relocated to Columbia between submission and review.

I don't know if anyone could have been more stunned than I was when the pink sheets arrived (they were indeed pink in those days) with a very good score and comments along the line of, well he's young and inexperienced, but he has some good ideas and he's working with good people. Those were the days.

Thus the second lesson here is that it is important to give new ideas and new and untried scholars a chance. Nay-sayers abound and should be ignored unless they provide concrete suggestions for improvement. Choose carefully who you listen to. Many a good idea has been strangled in the cradle. Treat all new ideas as infants – they cannot yet walk, don't expect them to run.

And we did show that infants under 5 pounds at birth born in hospitals with newborn intensive care units had mortality rates nearly a third lower than infants in other hospitals, accounting for all relevant confounders.

As my career developed I learned some other lessons. The first lesson is the primacy of the idea. All fields seem to divide themselves to some extent into the theoretical and the practical, or, as in physics, the theoretical and the experimental. In epidemiology, I think the dividing line puts hypothesis formulation and study design on one side, and execution and analysis on the other. Of course we need both, but I think that in recent years, there has been a tilt towards execution and analysis, shown most clearly in the emphases on what is considered important in judging randomized trials, which seem to leave aside such questions as to whether the hypothesis is sensible, the dosage correct in amount and timing or whether the underlying population is appropriate, in favor of statistical nuances. And another example is our current fascination with artificial intelligence and data mining with the implication that hypothesis formulation is merely an expression of the investigator's biases. Or the view that with a large enough sample size, we can solve any problem. In the lamented National Children's Study, all hypotheses were abandoned in favor of calling the

study an exercise in data collection. Its inevitable failure was pre-ordained at that moment.

Study design based on well-thought out hypotheses is at the core of successful epidemiology. Designing studies is one of the great joys of our field. How does one take a scientific idea and create an array of free-living individuals in the field with or without disease and use that array of people and information to draw a conclusion that will advance public health? That is always the challenge.

And I'd like to underline one of the most important study design questions - Who does our study design leave out? Who is missing? Some of you know the famous example of the mathematician Abraham Wald's recommendation to the military in WW II as to where airplanes needed reinforcing. Shown the locations of damage to planes that returned to base, he surprised the military by saying that reinforcement should be made in the parts of the airplanes that were *not* hit. Why? Because, he reasoned, planes hit in those parts were the ones that did not return to base. In our studies too, we are sometimes misled because we don't think enough about who is not in our study.

It is indeed fortunate for me that so many of the people who worked with me collaboratively to design studies are here either in person or on zoom or in our collective memories.

Mervyn Susser and Zena Stein are no longer with us, alas, though they lived to great ages, but I am so happy that their son Ezra Susser and their nephew Aryeh Stein are with us. This remarkable couple helped in every part of my early study designs, as did John Kiely who co-designed the next study, also funded by NIH, that showed that fetal deaths in labor were fewer in hospitals that had higher levels of intensive perinatal care.

Indeed this new technology, or perhaps we should say a new attention to the perinatal period by medicine, was really lowering mortality. So powerful an influence was it that the decade with the sharpest decline in neonatal mortality in the US in the 20th century was the 1970's, when newborn intensive care got underway.

The improvement in mortality led us to think about the disabilities that are unfortunately common in premature infants, and to design new studies that would investigate that question. In a series of papers with Mervyn, Zena and John Kiely, we predicted that this dramatically better survival would inevitably

translate into higher number of handicapped children, a conclusion resisted then by many neonatologists. That prediction did in fact come true, but it looks as though for cerebral palsy at least, the prevalence has started to decline in the 21st century.

The new focus on disability produced a whole series of studies beginning with the neonatal brain hemorrhage study, conducted with Jennifer Pinto-Martin which began with newborns and had at least four rounds of NIH supported follow-up studies taking the children into their twenties, each focusing on a different aspect of health and development. I am happy to say that these studies helped to launch Jennifer's great career in autism epidemiology.

And then I was fortunate to collaborate with Alan Leviton and Karl Kuban as we built first the Developmental Epidemiology Network, and then, joined by Olaf Dammann and Michael O'Shea, the Extremely Low Gestational Age Newborn Study (ELGAN) that is still in the field, examining these babies who had been born three months early who are now age 18.

And when I came to Michigan, I developed along with Saroj Saigal, John Tyson and Madeleine Lenski, a study comparing outcomes for low birthweight infants in five population-based international cohorts – in the US, Canada, Germany, Holland

and Jamaica. Jack Lorenz was also involved and led a most important paper from that study, showing that mortality rates for very small infants were higher in Holland, but disability rates were lower.

And then circumstances moved us away from low birthweight newborns into the broader population of children, as the National Children's Study, which we entered with great hopes, creating a consortium of MSU, the University of Michigan, Wayne State, Henry Ford and our health department to conduct the study, we began to recruit unselected pregnancies, moving our focus also into the prenatal period.

As noted earlier, the National Children's Study collapsed, and was replaced by the ECHO study which we are currently attempting to renew. In these efforts, Jean Kerver was my essential colleague, serving first as a project director of the National Children's Study, and then as a co-investigator, and now as the contact co-Principal investigator of the large ECHO study. And we are both bolstered by a superb group of young field operatives led by Alexa Drew and Breanna Kornatowski, not to mention wonderful scientific collaborators throughout our state.

And then came COVID. I knew Mike Joyner and Arturo Casadevall from our joint work trying, not very successfully so far, to put a dent in the at times rabid enthusiasm for the human genome project and its alleged benefits to mankind. Thus when Arturo began to talk about the potential of convalescent plasma, a topic on which he has been writing for nearly 30 years, to make a difference to COVID outcome, we created an organization nearly overnight that included hundreds of physicians, a website directed here by MSU, and a 7-person leadership team that initially studied the effect of convalescent plasma and then, convinced it had a role to play, began to advocate for its broader use.

And this study returned me to a conclusion that was nearly 50 years old. Randomized trials may be at the top of our research design hierarchy, but they do not constitute the entirety of evidence, and they can go badly wrong when not informed by the best science. Physicians who provided convalescent serum to their patients in the great age of passive antibody treatment, the 1890's to the 1930's, would have been surprised indeed to see trials mounted of convalescent plasma in COVID-19 in hospitalized patients on ventilators weeks after the onset of disease. Their mantra was treat in the first three days of illness or forget about it. And they would have been shocked to see eminent medical authorities and institutions pay more attention to large poorly conceptualized studies that did not

show effectiveness than to smaller but more carefully designed studies, done earlier in the illness course, that showed substantial effectiveness.

This quick overview of a lifetime of research underlines what may be perhaps the most important lesson of all – the value of colleagues. It is conventional to refer to many activities as team sports, but, as documented in my career, Epidemiology is truly all about teamwork. Successful epidemiology is achieved only by working together.

And I include here colleagues whom one does not work with directly, but who we see at intervals – at scientific meetings, at guest lectures or on panels assembled for a special purpose or just by reading their papers. I met Bernard Dan when Madeleine and Alan Leviton and I among others were gathered to try to attach a solid definition to the ancient term, Cerebral Palsy. We published that definition in 2005, revised it slightly in 2007, and these two papers have been cited nearly 10,000 times. And I haven't been in the same room with Allen Wilcox – even if that room was a coffee shop or a bar – where I did not learn something new and interesting. That so many of my colleagues are here today in person or on zoom gives me great joy.

And then one learns from students, who are too many to name, but among our speakers are some who have been in classes of mine – Jean Kerver, Mary Jo Cooley Hidecker, Ting Hong, Crystal Tyler. They and other students of mine have shown by their own work and careers how much they have to teach and contribute to science and public health.

And even the monk-like library work that I advocated a few minutes ago is not truly solitary, because it puts you into conversation with people who lived and worked long ago, many of whom did remarkable science.

So if I had to summarize what I have learned for the benefit of someone entering the field now, I would say:

1. Prepare yourself – get lost in conversation with the scientists who preceded you. The library houses some of your best friends, and the farther you go back in time the more interesting these friendships become.
2. Do not fear a new idea, even if, perhaps especially if, it conflicts with conventional wisdom and is dismissed by individuals who have not really examined it closely. And always remember that it is ideas that drive data collection not the other way around.

3. Seek out supportive mentors. Not yes people, but genuinely critical people who know how to help shape a new idea to make it into a realistic study, workable in the field. Learn to distinguish nay-saying from intelligent criticism.
4. Try as much as possible to study representative samples or at least samples of people that don't leave too many people out. Vital data are epidemiologic gold mines.
5. In making decisions, be they for clinical or public health purposes, use all available information. Randomized trials are great, but they do not constitute the entirety of evidence, and they can sometimes mislead.
6. In choosing what studies to undertake, allow yourself to prioritize ventures that have real potential to lead to public health improvement.

And lastly, and most importantly, as shown here today, collegiality and collaboration are the lifeblood of epidemiologic science. Do your best to work with good people and to meet people who share common interests. Attend lectures, go to meetings, initiate friendships, create teams. Do not hesitate to approach senior people with questions or conversation. And at the same time, do not hesitate to bring an eager young person who knows little or nothing into the fold.

And thanks to each and everyone of you for doing me the great honor of participating in this memorable event.